بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 11

Antibiotics Pt.3

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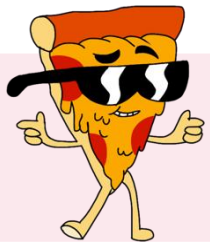


Natural Penicillins

Given IV / IM ← (penicillin G, penicillin VK) → Given orally

Gram-positive

pen-susc *S. pneumoniae*

Group A/B/C/G strep

viridans streptococci

Enterococcus

Gram-negative

Neisseria sp. Neisseria meningitidis

Anaerobes

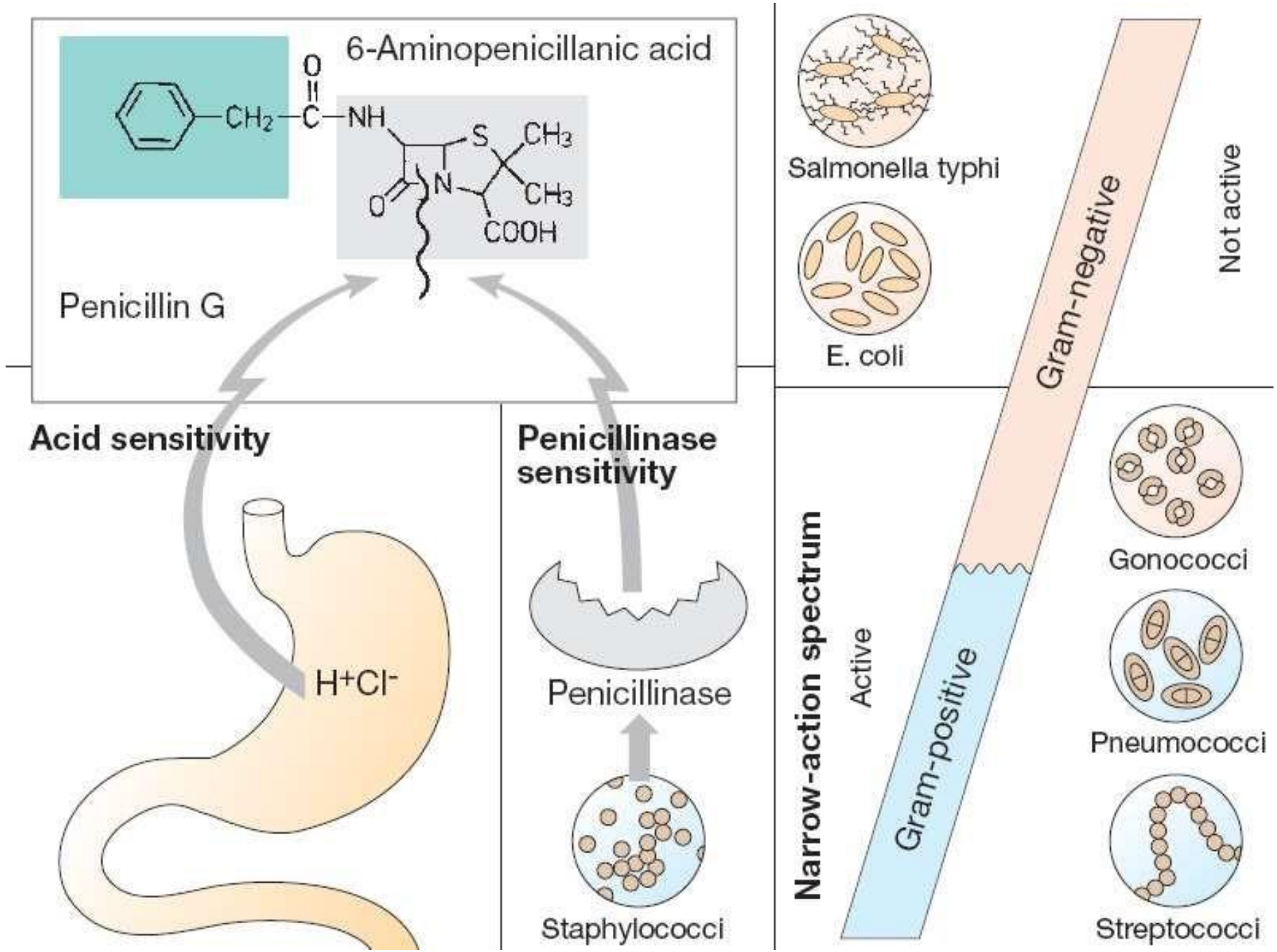
Above the diaphragm

Clostridium sp.

Other

Treponema pallidum (syphilis)

This is called the Penicillin spectrum; which means the bacteria inwhich the penicillin is active against.


6-Aminopenicillanic acid
Penicillin G
Acid sensitivity
Penicillinase sensitivity
H+Cl-
Penicillinase
Staphylococci
Salmonella typhi
E. coli
Gram-negative
Not active
Narrow-action spectrum
Active
Gram-positive
Gonococci
Pneumococci
Streptococci

Natural Penicillins

- Natural penicillins have a narrow therapeutic index.

❖ **Empirical use:**
Natural penicillins can be used empirically to treat infections of the oral cavity (Notice that it covers all of the possible causative agents of the oral infections).

❖ **Definitive use in meningitis:**
Natural penicillins can be used in meningitis only after the culture confirms ***Neisseria meningitidis*** as the causative organism, (since it is only causative agent of meningitis its acrive against).

➢ **De-escalation strategy:**
In cases of meningitis, treatment usually starts with a broad-spectrum antibiotic for the first 3–4 days. Once culture results are available, **de-escalation is performed, switching to penicillin.**

- Route of administration in meningitis:
In meningitis, a high concentration of antibiotic is required in the brain. Therefore, penicillin G is given **intravenously (IV) to achieve adequate CSF levels**. Penicillin V is **not** used **because it does not achieve sufficient concentrations in the CSF.**

Benzathine penicillin

Benzathine penicillin is a long-acting intramuscular depot formulation of penicillin G combined with chemical compounds, which provides sustained low plasma levels for approximately 3–4 weeks

- **Benzathine penicillin for intramuscular injection yield low but prolonged drug levels.**
- **A single intramuscular injection of benzathine penicillin, 1.2 million units, is effective treatment for beta–hemolytic streptococcal pharyngitis;**
- **Also prophylactic, given intramuscularly once every 3–4 weeks, it prevents re-infection..**
- **Reoccurrence of rheumatic fever.**
- **Benzathine penicillin G, 2.4 million units intramuscularly once a week for 1–3 weeks, is effective in the treatment of syphilis. Also prophylactic.**

Streptococcal Pharyngitis (Strep Throat) and Rheumatic Fever

1. Streptococcal Pharyngitis (Strep Throat)

There is a condition called **streptococcal pharyngitis (strep throat)**, which occurs in the **oral cavity (pharynx).** Pharyngitis can be caused by many organisms, but one of **the most common and important causes is Streptococcus pyogenes and thus we call it "strep throat".**

Characteristics of Strep Throat:

- Common especially in children
- Characterized by white **circular patches (abscesses)** on the ceiling of the throat
- Strep throat is caused specifically by ***Streptococcus pyogenes.***

2. Treatment of Strep Throat

Strep throat is a monomicrobial infection (one main causative organism).

Empirical = Definitive therapy

Because there is only one predictable cause, the empirical treatment is the same as the definitive treatment.

- We give Penicillin V (oral) or Penicillin G
- This is similar to **odontogenic infections,** where the causative organism is **also known and we give the patient penicillin G or V.**

Streptococcal Pharyngitis (Strep Throat) and Rheumatic Fever

3. Risk of Rheumatic Fever

If 100 people get strep throat, 1–2% will develop rheumatic fever. In some populations (e.g., India), this may reach ~5%

Timing : Symptoms of Rheumatic fever usually **appear about 4 weeks after the initial infection.**

4. Why Does Rheumatic Fever Occur?

Rheumatic fever is **NOT caused by direct bacterial invasion**. It is caused by **antigenic mimicry.**

❑ Antigenic Mimicry

- Some streptococcal **antigens** (especially **M protein**) look like the **human proteins (antigens).**
- When the immune system produces **antibodies against strep antigens**, these antibodies cross-react with the body's own tissues leading to an auto-immune condition.

5. Organs Affected by this Autoimmune Reaction

The immune system attacks tissues that resemble streptococcal antigens:

1) **Brain (Hypothalamus) --> causing fever**
2) **Synovial fluid in joints --> Causing rheumatoid (pain and swelling of joints)**
3) **Heart valves**

This autoimmune reaction **results in rheumatic fever.**

Streptococcal Pharyngitis (Strep Throat) and Rheumatic Fever

6. Why Is Recurrent Rheumatic Fever Dangerous?

If a patient develops rheumatic fever once, the immune system **develops memory (B cells and immune cells now recognize the antigen).**

- On re-exposure:
  - The immune response is **faster and stronger.**
  - Damage is **more severe.**
  - Organs (like the **heart, brain, joints, and even the kidney**) are at **higher risk during the recurrence of the fever.**

  This is why a second episode is **much more dangerous than the first.**

7. Why Only Some People Develop Rheumatic Fever?

Only 1–2% of patients develop rheumatic fever due to **genetic polymorphism.**
Genetic Explanation

- Single nucleotide polymorphisms (SNPs) in some individuals may increase the antigenic similarity between streptococcal antigens and human antigens leading to stronger autoimmune cross-reactivity (rheumatic fever).

Streptococcal Pharyngitis (Strep Throat) and Rheumatic Fever

8. Management After the Development of Rheumatic Fever

Once a patient is diagnosed with rheumatic fever, **it is essential to prophylact the patient to prevent recurrent streptococcal infection and recurrent rheumatic fever**, which can lead to **severe and permanent complications.**
Management consists of two mandatory steps:

Step 1: Eradication of Streptococcal Infection

Even if the initial throat infection has resolved, the patient must receive eradication therapy to eliminate any residual Streptococcus pyogenes and to stop further antigenic stimulation.

- Drug used: **Benzathine penicillin (IM)**
- Dose: **1.2 million units**
- Frequency: **Single injection**

Rationale

- Benzathine penicillin G is a long-acting depot preparation
- It forms a colloid-like suspension in muscle (Releases penicillin slowly over approximately 28 days)

Step 2: Secondary Prophylaxis

After eradication, the patient must be **prophylacted to prevent re-infection with Streptococcus pyogenes and to avoid recurrence of rheumatic fever.**

- Drug used: **Benzathine penicillin (IM)**
- Dose: **1.2 million units**
- Frequency: **Every 3–4 weeks, Duration:** 20–30 years (or lifelong in some patients).

Tonsillitis & Syphilis

Tonsillitis and Use of Benzathine Penicillin

children commonly develop **tonsillitis**. The most common bacterial causes of tonsillitis are **Streptococcus pneumoniae** and **Streptococcus pyogenes**

In some children, tonsillitis or pharyngitis becomes **recurrent**. In these cases, **post-treatment suppression therapy may be used to reduce the bacterial load.**

- Drug Used : **Benzathine penicillin G**
- Dose: **1.2 million units**
- Route: **Intramuscular (IM)**
- Frequency: **One injection every month**
- Duration: **Up to 6 injections (approximately 6 months)**

If Suppression Therapy Fails

If recurrent infections persist despite benzathine penicillin injections, **we preform Tonsillectomy (Surgical removal of the tonsils)**

Use of Benzathine Penicillin in Syphilis

Cause of Syphilis: **Treponema pallidum**

In syphilis, the dose of **benzathine penicillin G** must be increased (up **to 2.4 million units**) **because the minimum inhibitory concentration (MIC) of Treponema pallidum is higher than that of streptococci.** Therefore, higher doses are required to achieve effective bacterial killing.

Important Pharmacological Principles

- Different microorganisms have different MIC values for the same antibiotic
- The same drug can be dosed differently depending on:
  - The causative microorganism.
  - The site of infection.

Natural penicillin

- **Benylpenicillin (Penicillin V) is more acid stable, is orally active but is less potent than penicillin G.**

- **Penicillin V often employed in the treatment of oral infection, where it is effective against some anaerobic organism.**

- ***Penicillin V is the most frequently prescribed* antibiotic for oral infections.**

- **It is the first choice in the treatment of odontogenic infections.**

(1) post extraction infection,

(2) pericoronitis and

(3) salivary gland infection

b-lactamase-resistant Penicillins

- These include Cloxacillin, Flucloxacilin, Oxacillin which are well-absorbed orally.
- They also includes methicillin (not available any more).
- Antibacterial spectrum is the same as for penicillin G, but less potent.
- Their use is restricted to treatment of infections caused by penicillins-resistant bacteria. Nonetheless, Many *Staphylococci* are now resistant to them.

b-lactamase-resistant penicillin

Early Use of Penicillin and the Emergence of Resistance

In the early period of penicillin use, specifically penicillin G and penicillin V, many patients—especially during World War II—had skin wounds. Staphylococcus aureus, which is normally found on the skin, was able to enter the body through these wounds.

Development of Resistance in Staphylococcus aureus

One of the main reasons for the reduced effectiveness of penicillin G and V was that Staphylococcus aureus began **producing β-lactamase (penicillinase)**. β-lactamase enzymes cleave the β-lactam ring and inactivate penicillin (This represents a mechanism of resistance)

As a result:

- **The spectrum of penicillin G and penicillin V does NOT include *Staphylococcus aureus*,** Even though *S. aureus* is Gram-positive.

Development of β-Lactamase-Resistant Penicillins (Around 1960)

In 1960, β-lactamase-resistant penicillins were developed to protect the β-lactam ring from degradation by β-lactamase enzymes

- These penicillins:
  - **Have the same antibacterial spectrum as penicillin G.**
  - **Plus added activity against *Staphylococcus aureus*.**

Penicillinase-Resistant Penicillins

(nafcillin, oxacillin, methicillin)

Developed to overcome the penicillinase enzyme of *S. aureus* which inactivated natural penicillins

Gram-positive

Methicillin-susceptible *S. aureus*

Penicillin-susceptible strains of Streptococci

Penicillinase-resistant penicillins are used to treat cellulitis (a bacterial infection of the skin and the soft tissue beneath it) and they are given empirically to cover the common causative microorganisms responsible for skin infections.

Common Bacteria by Site of Infection

Penicillinase-resistant penicillins are used empirically and sometimes definitely here.

Mouth
Peptococcus
Peptostreptococcus
Actinomyces

Skin/Soft Tissue
S. aureus
S. pyogenes
S. epidermidis
Pasteurella

Bone and Joint
S. aureus
S. epidermidis
Streptococci
N. gonorrhoeae
Gram-negative rods

Abdomen
E. coli, Proteus
Klebsiella
Enterococcus
Bacteroides sp.

Urinary Tract
E. coli, Proteus
Klebsiella
Enterococcus
Staph saprophyticus

Upper Respiratory
S. pneumoniae
H. influenzae
M. catarrhalis
S. pyogenes

Lower Respiratory Community
S. pneumoniae
H. influenzae
K. pneumoniae
Legionella pneumophila
Mycoplasma, Chlamydia

Lower Respiratory Hospital
K. pneumoniae
P. aeruginosa
Enterobacter sp.
Serratia sp.
S. aureus

Meningitis
S. pneumoniae
N. meningitidis
H. influenza
Group B Strep
E. coli
Listeria

Extended Spectrum Penicillins

- **These include Ampicillin, which is fairly well absorbed orally, Amoxicillin which is very well absorbed, and is prodrug to ampicillin.**

- **Their antibacterial spectrum is the same as for penicillin G plus some Gram-negative bacteria. (**Enhanced ability to penetrate the gram-negative outer membrane).

- **Ampicillin and amoxicillin are among the most useful antibiotics for treating children suffering from infections caused by sensitive gram-negative aerobic bacteria, *enterococci, and β-lactamase-negative H. influenzae.***

Aminopenicillins
(ampicillin, amoxicillin)

Developed to **increase activity against gram-negative aerobes**

Gram-positive

pen-susc *S. aureus*

Pen-susc streptococci

viridans streptococci

Enterococcus sp.

Listeria monocytogenes

Gram-negative

Proteus mirabilis

Salmonella,

some *E. coli*

βL- *H. influenzae*

β lactamase negative H.influenzae (H.influenzae that don't produce β lactamase

β-Lactamase Inhibitor Combos
(Unasyn, Augmentin, Timentin, Zosyn)

Developed to gain or enhance activity against β-lactamase producing organisms (some better than others). Provides some or good activity against:

Gram-positive

S. aureus (MSSA)

Anaerobes

Bacteroides sp.

Gram-negative

H. influenzae

E. coli

Proteus sp.

Klebsiella sp.

Neisseria gonorrhoeae

Moraxella catarrhalis

Aminopenicillins

Formation: By adding an amino group to penicillin, we obtain aminopenicillins. We have two main drugs

- Ampicillin
- Amoxicillin

Spectrum: Aminopenicillins have expanded activity against Gram-negative bacteria compared to natural penicillins.

β-Lactamase and H.influenzae

- β-lactamase-negative H.influenzae refers to strains that do not produce β-lactamase and are therefore susceptible to aminopenicillins. However, many strains of H. influenzae and Moraxella catarrhalis have learned to produce β-lactamase. As a result, aminopenicillins alone are not active against these β-lactamase-producing organisms (including staph.aureus).
- Solution: Addition of Clavulanic Acid (β-lactamase inhibitor). It is added to aminopenicillins to protect them from β-lactamase degradation. Resulting in new combination drugs, the most common being Augmentin (amoxicillin + clavulanic acid).
- These combinations are active against:
  - All *Haemophilus influenzae* (including β-lactamase producers).
  - Moraxella catarrhalis.

Clinical Use of Aminopenicillin–Clavulanate Combinations

Empirical use

- Aminopenicillin + clavulanic acid (e.g., Augmentin) is used **empirically to cover upper respiratory tract infections.**
- **It covers the common causative agents of upper respiratory tract infections.**
- Augmentin is considered the drug of choice for treating upper respiratory tract infections.

Use in Skin Infections

- Although Augmentin can cover the causative organisms of skin infections, **it is not preferred. Because we must always use the narrowest effective spectrum.** Therefore, Augmentin is generally not used for skin infections when narrower-spectrum options are available.

Spectrum and Gastrointestinal Side Effects

- Increased antibiotic coverage **leads to greater disturbance of normal gastrointestinal flora and increased incidence of diarrhea**
- Augmentin causes more diarrhea than penicillin V
- Amoxicillin causes more diarrhea than penicillin V

Use of Amoxicillin Alone

Sometimes amoxicillin is used alone without clavulanic acid. Why?

- For **definitive treatment when the causative organism is known**
- To cover a narrower spectrum than Augmentin.

Key Pharmacological Principles

- **Adding clavulanic acid broadens the spectrum but increases side effects**
- Broader spectrum ≠ better treatment
- Always choose the **narrowest effective antibiotic**

Broad Spectrum Penicillins

- They are widely used in the treatment of respiratory infections.
- Are given orally to treat sinusitis, otitis, and lower respiratory tract infections.
- Amoxicillin is the favored drug for the treatment of acute otitis. Empirical (Increase the dose to 80-90 mg/kg/day).
- Ampicllin is the most active of the oral beta-lactam antibiotics against penicillin-resistant pneumococci and are the preferred beta-lactam antibiotics for treating infections suspected to be caused by these resistant strains.

Broad Spectrum Penicillins

1. The Evolution of Anti-Pseudomonal Penicillins

To effectively treat Gram-negative infections, penicillins had to be modified to penetrate the **outer membrane** (the "second membrane") of these bacteria. This led to two major classes:

a) Carboxypenicillins (e.g., Ticarcillin, Carbenicillin)

b) Ureidopenicillins (e.g., Piperacillin)

Carboxypenicillins (e.g., Ticarcillin, Carbenicillin)

- **Trade-off:** These drugs lost significant activity against Gram-positive bacteria but gained powerful activity against **Gram-negative** organisms.
- **Key Coverage:** ***Pseudomonas aeruginosa, Proteus, some E. coli, Enterobacter, \beta-lactamase producing H. influenzae, Salmonella, and Shigella. (Check slides***
- **Clinical Note:** Ticarcillin is historically noted as the most powerful agent specifically against Pseudomonas aeruginosa.
- **Administration:** These are poorly absorbed from the GI tract and are strictly **injectable**.

Broad Spectrum Penicillins

Ureidopenicillins (e.g., Piperacillin)

- **Progression:** These offer a broader Gram-negative spectrum than carboxypenicillins.
- **The Tazobactam Addition:** While Piperacillin is potent, it is **vulnerable to beta-lactamases.** Adding Tazobactam (a beta-lactamase inhibitor) restores and expands its activity to include:

1) **MSSA (Methicillin-sensitive S. aureus)** – Note: **Piperacillin alone does not cover MSSA.**
2) **Anaerobes (e.g., Bacteroides).**
3) **Klebsiella and other \beta-lactamase producing strains.**

Lower Respiratory Tract Infections (LRTI)

- **Piperacillin/Tazobactam** is a staple for **hospital-acquired LRTIs (lower respiratory tract infections)** because it covers almost all likely pathogens, including:

  Klebsiella, Pseudomonas, Serratia, and Enterobacter.

  The MRSA Exception: No single "super-antibiotic" covers everything. This combination does not cover MRSA.

- **Empiric Strategy:** In a hospital setting, clinicians often use Piperacillin/Tazobactam + an MRSA agent (like Vancomycin or Linezolid) to ensure full coverage until cultures return.

The "Pseudomonas" Challenge

Treating Pseudomonas aeruginosa is difficult for two reasons:

1. **Resistance Development:** The pathogen can develop resistance during the course of therapy. Even if the initial culture says "sensitive," the bacteria can adapt.

2. **Mortality:** Monotherapy for Pseudomonas carries a high mortality rate (often cited near 50% in severe cases).

The Rule: Writing a prescription for an anti-pseudomonal penicillin alone is usually insufficient. It should be paired with an Aminoglycoside or a Fluoroquinolone for synergy and to prevent resistance.

3. Principles of Antibiotic Stewardship

Culture & AST: Always wait for the Culture and Antimicrobial Susceptibility Testing (AST) results.

De-escalation: Once the definitive pathogen is identified, switch from the broad-spectrum drug (like Pip/Tazo) to the narrowest spectrum antibiotic possible to prevent further resistance.

4. Safety and Hypersensitivity

Penicillins are generally very safe with few direct toxic side effects, but they are notorious for hypersensitivity reactions.

The Mechanism

When penicillin is administered, it degrades into metabolic products. These products bind to proteins in the human body, acting as a hapten. This protein-drug complex triggers the immune system.

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The Mechanism

When penicillin is administered, it degrades into metabolic products. These products bind to proteins in the human body, acting as a hapten. This protein-drug complex triggers the immune system. (See next slide).

Classification of Reactions

Type 1 (Immediate): The most dangerous. Includes anaphylaxis, bronchoconstriction, and hypotension.

Type 2 (Delayed): Generally less life-threatening, often manifesting as a skin rash.

Protocol: Always perform a skin test if an allergy is suspected. Never prescribe penicillin without checking the patient's sensitivity history.

Broad Spectrum Penicillins

- **Amoxicillin is employed prophylactically, for patient with abnormal heart valves who are undertaken extensive oral surgery.**
- **(the drug of choice for prophylaxis of infective endocarditis).**

Extended Spectrum Penicillins

- These include Carbenicillin, Ticarcillin, and Piperacillin.
- All are very poorly absorbed from the gut. They are susceptible to b-lactamases.
- Their antibacterial spectrum is the same as the broad-spectrum drugs plus pseudomonads.
- These antibiotics are used in the treatment of urinary tract, lung, and bloodstream infections caused by ampicillin-resistant enteric gram-negative pathogens.

Extended Spectrum Penicillins

Piperacillin has increased potency against common Gram- negative organisms.

Its main uses are in intensive care medicine (pneumonia, peritonitis)

- **Although supportive clinical data are lacking for superiority of combination therapy over single-drug therapy, because of the propensity of *P aeruginosa* to develop resistance during treatment, an antipseudomonal penicillin is frequently used in combination with an aminoglycoside or fluoroquinolone for pseudomonal infections outside the urinary tract.**

Carboxypenicillins
(carbenicillin, ticarcillin)

Developed to further increase activity against resistant gram-negative aerobes

Gram-positive	**Gram-negative**
marginal	*Proteus mirabilis* *Salmonella, Shigella* some *E. coli* βL- *H. influenzae* *Enterobacter sp.* *Pseudomonas aeruginosa*

Ureidopenicillins
(piperacillin, azlocillin)

Developed to further increase activity against resistant gram-negative aerobes

Gram-positive

viridans strep
Group strep
some Enterococcus

Anaerobes

Fairly good activity

Gram-negative

Proteus mirabilis
Salmonella, Shigella
E. coli
βL- *H. influenzae*
Enterobacter sp.
Pseudomonas aeruginosa
Serratia marcescens
some *Klebsiella sp.*

β-Lactamase Inhibitor Combos
(Unasyn, Augmentin, Timentin, Zosyn)

Developed to gain or enhance activity against β-lactamase producing organisms (some better than others). Provides some or good activity against:

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S. aureus (MSSA)

Anaerobes

Bacteroides sp.

Gram-negative

H. influenzae

E. coli

Proteus sp.

Klebsiella sp.

Neisseria gonorrhoeae

Moraxella catarrhalis

Unwanted effects

- **Penicillins are remarkably free of direct toxic effects.**
- **The main unwanted side-effects are hypersensitivity reactions which derive from the fact that degradation products of penicillins combine with host proteins and become antigenic.**
- **They cause alteration of bacterial flora in the gut and this can be associated with GI disturbances, such as Diarrhoea. (happened to a greater extent with those have an extended antibacterial spectrum).**
- **All Penicillins, particularly Methicillin, have the potential to cause acute nephritis, thus Methicillin is no longer available.**

Unwanted effects

- **Neurotoxicity**

- **Antiseudomental penicillins (Carbenicillin and Ticarcillin), to some extent Penicillin G, may decrease agglutination.**

- **All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food. Exception being amoxicillin.**

Ampicillin: Only effective in injectable form (oral absorption is too poor for serious systemic infections).

Carboxypenicillins/Ureidopenicillins: Strictly injectable due to poor GI absorption.

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

1. Doctor’s Lecture
2. I used AI to organise the Notes.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			